REMARKS

The applicants thank the Examiner for the thorough examination of the application. No new matter is believed to be added to the application by this Amendment.

Status Of The Claims

Claims 1-24 are pending in the application.

Rejection Under 35 U.S.C. §103(a) Over Griffin And Biegajski

Claims 1-24 are rejected under 35 U.S.C. §103(a) as being unpatentable over Griffin (EP 0 010 987) in view of Biegajski (U.S Patent 5,700,478). Applicants traverse.

Distinctions of the invention over Griffin have been discussed in the Amendments filed December 7, 2005 and June 15, 2005. For brevity, these discussions are not repeated here.

Griffin fails to disclose any active substance-containing layers having a non-uniform concentration or a non-uniform width in relation to the longitudinal extension. In contrast, claim 1 of the present invention recites "at least one of the parameters of width and concentration of the active and/or auxiliary substance of this layer is not constant in relation to said longitudinal extension." Throughout the whole document, Griffin discusses that the active substance (or medicament) is dispersed or distributed uniformly within the erodable sheet (*see* Griffin at p. 3, lines 12-15; p. 4, lines 20-27; p. 9, lines 3-6; p. 10, lines 4-5, 29-30; p. 12, Example 1, in particular, lines 8-9 "to ensure uniformity"; claim 1). Likewise, and even more so, Griffin fails to disclose a matrix layer having a non-uniform width. In conclusion, Griffin fails to disclose a drug delivery device in which at least one of the parameters of width and concentration of the active

and/or auxiliary substance is not constant in relation to the longitudinal extension of the active substance-containing layer.

Furthermore, with respect to the limitation "wherein at least one of said layers comprises a liquid soluble adhesive which dissolves when the preparation is exposed to a body fluid" (claim 1 of the present invention), the Examiner relies page 8, lines 1-9, of Griffin. However, this passage notes that certain polymers used in the sheets of the device may be sticky, and this stickiness is considered disadvantageous as it prevents the sheet from fully unfolding immediately when it arrives in the rumen (*see* Griffin at p. 8, lines 5-6: "to ensure that the sheet fully unfolds when in the rumen"). To counteract this tendency of stickiness, Griffin recommends to provide the sheet with a water-soluble coating, e.g., water-soluble paper, or to interleave the devices with water-absorbing sheets (*see* Griffin at p. 8, lines 3-9). Hence, Griffin teaches that stickiness of the sheets should be avoided, contrary to what is required in the last paragraph of instant claim 1 (and likewise in claim 20) of the present invention. Therefore, Griffin teaches away from the invention as presently claimed.

A prior art reference must be considered in its entirety, i.e., as a <u>whole</u>, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984). It is improper to combine references where the references teach away from their combination. *In re Grasselli*, 713 F.2d 731, 743, 218 USPQ 769, 779 (Fed. Cir. 1983). A *prima facie* case of obviousness may also be rebutted by showing that the art, in any material respect, teaches away from the invention. *In re Geisler*, 116 F.3d 1465, 1471, 43 USPQ2d 1362, 1366 (Fed. Cir. 1997).

The skilled person, upon reading Griffin (in particular, the 1st paragraph on page 8 of Griffin), would certainly not have considered incorporating an adhesive into one of the layers. Griffin teaches that anything should be done to ensure that the device would unroll quickly when in the rumen. This means to avoid using sheets having adhesive surfaces, and in case of adhesiveness, using additional approaches (water-soluble coatings etc.) to reduce or eliminate adhesiveness.

At page 3, lines 14-16 of the Office Action, the Examiner states: "The inclusion of a pressure-sensitive adhesive however would be obvious to an artisan of ordinary skill since they would want the unfolded patch to adhere to the delivering surface." However, this statement is purely speculative and runs counter the whole teaching of Griffin. As noted above, Griffin considers stickiness of the sheet as an undesirable effect, as it interferes with the unfolding of the device. Furthermore, according to the teaching of Griffin, the unfolded flat shape of the device (the "second shape" mentioned on p. 3, lines 12-21 of Griffin) serves to retain the device in the rumen of the animal by preventing its passage out of the rumen, due to the enlarged size of the device (*see* Griffin at p. 1, lines 17-23; p. 2, lines 25-32; p. 3, lines 12-21; p. 6, lines 8-18). On the other hand, Griffin fails to provide any hint suggesting that the device should adhere to the inner surface of the rumen.

Since Griffin teaches away from incorporating any adhesives into a layer of the preparation, or at least could not provide any motivation for doing so, the disclosure of Biegajski is not considered relevant. That is, Biegajski fails to address the deficiencies of Griffin.

In Biegajski the water-soluble pressure-sensitive adhesives serve a function that is different from the function of the adhesives recited in the last sub-paragraph of instant claim 1 of

the present invention. Biegajski relates to adhesives that are used to affix a device to a mucosal surface, i.e., the mucosa-lined surface of a body cavity (*see* Biegajski at col. 1, lines 1-37; col., 3, lines 15-22). In contrast, the liquid-soluble adhesive which is present in at least one of the layers of the device according to the present invention serves to interconnect the adjacent layers (e.g., in the wound-up configuration shown in Fig. 1 a/b) to ensure that the device, when exposed to body fluid, unrolls partially and slowly (see present specification, p. 6, 2nd paragraph).

FIG.1

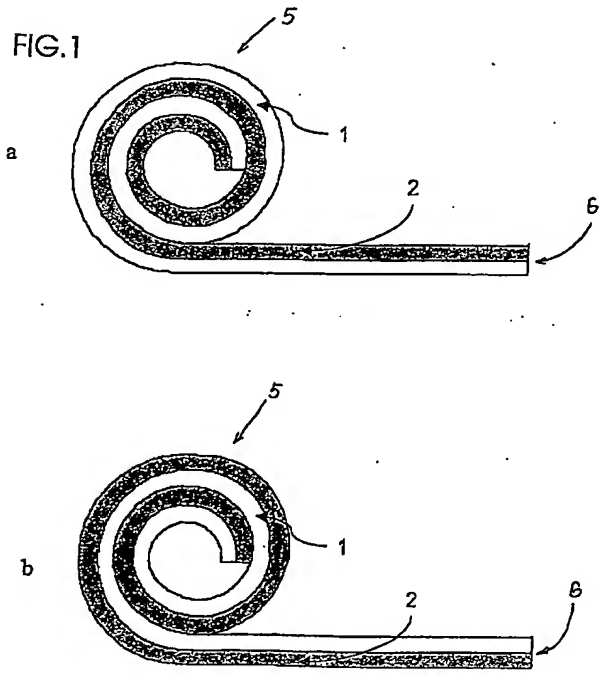

Fig 1a/b of the Present Invention

Likewise, Griffin fails to mention adhesion to mucosal surfaces. Therefore, in addition to the above-mentioned reasons, there was no motivation to combine Biegajski with Griffin. Neither Griffin nor the present invention pertains to providing a drug delivery device with mucoadhesive properties. Therefore, the Examiner has no basis for the conclusion set forth in the Office Action at p. 4, 1st par., saying that it would have been obvious "to include the pressure-sensitive adhesive layers of '478 [Biegajski] into the rolled device of '987 [Griffin] in

order to insure a preferred [?] release and adherence to the specific application situs." Even if such modification would have been considered, this would still not have resulted in a preparation as defined in claim 1 of the present invention because none of the cited documents teach limitation (b) "at least one of the parameters ... is not constant in relation to said longitudinal extension."

Similarly, the Examiner asserts at p. 4, last par. of the Office Action that "it would have been obvious to include the pressure sensitive adhesives of the '478 [Biegajski] patent into the carriers of the rolled device of '987 [Griffin] in order to provide a specific release of active agent and to adhere to the body internally." This rationale fails for the same reasons as discussed above. Griffin advises against incorporating any adhesives, as adhesiveness is considered disadvantageous (*see* Griffin at p. 8, 1st par.). In addition, it is unclear and speculative how incorporation of adhesives into the devices of '978 would "provide a specific release of active agent." Also, there is no motivation to incorporate an adhesive "to adhere the device to the body internally" since according to the teaching of Griffin, the device is retained in the body (in the rumen of an animal) by the size of its "second shape" (unfolded/unrolled; Griffin at p. 3, lines 12-21).

At page 4 of the Office Action (paragraph 4), the Examiner asserts that: "the device of the reference performs identically to that of the instant claims." However, the device described by Griffin is present in only two shapes: in a first shape in which the sheet is constrained, and in a second shape in which the sheet is unfolded or unrolled (Griffin at p. 3, lines 12-21). According to Griffin, it is advantageous for the device to unfold immediately after it has arrived in the rumen of an animal, as the unfolded state helps to retain the device in the rumen (Griffin at p. 3,

lines 12-21; p. 6, lines 15-22). As the medicament is distributed uniformly throughout the erodable polymer layer (Griffin at p. 3, lines 12-15), it is always released from the entire surface of the device after the device has been unfolded or unwound. The overall rate and duration of active substance release may be adjusted by using materials having different erosion characteristics (Griffin at p. 5, lines 6-14). However, using a non-uniform width of the active substance containing layer or non-uniform concentration of the active substance within this layer (as defined in present claim 1) would not affect the release characteristics of Griffin's device, which unfolds completely as soon as it has arrived in the rumen, due to the fact that the medicament is released from the entire surface of the device. Griffin fails to teach active substance release from a partially unrolled device (present specification at p. 6, 2nd par.), and also fails to teach retarding the unrolling process by using adhesives (present specification at p. 6, 2nd par.). Therefore, due to the constructional features set out in claim 1, the device of the present invention necessarily performs differently from the devices taught by the related art.

The drug release devices of the present invention are suitable to provide any desired release profile. In the present invention, the release profile relates to the time-controllable release of active substances from a preparation. The release kinetics clearly indicate that the release of active substance is to be controlled in a time-dependent manner. According to the present invention, the release profile is controlled by the geometry of the active substance-containing layer (e.g., non-uniform geometry, such as is set forth in claim 1) and the rate of the unrolling process (specification at p. 6, 2nd par.). Alternatively, concentration gradients in the longitudinal direction may be used for obtaining a desired release profile (specification at p. 5, 4th paragraph and claim 6). The rate of the unrolling (or unwinding) process may be controlled

according to the present invention by selecting materials having the required solubility or degradability, by adjusting the thickness of the layers, or by selecting an adhesive having the desired solubility (*see* specification at p. 5, 2nd and 3rd par.; p. 6, 2nd par.; claims 5 and 10). Thus, it is ensured that the device unrolls or unfolds slowly or gradually, contrary to the teaching of Griffin. Also, claims 20 and 21 of the present invention recite predeterminable release kinetics and release schedule.

Based on the teachings provided in Griffin and Biegajski, one of ordinary skill in the art would not be motivated to provide a layer of a rolled or folded laminate with a liquid-soluble adhesive which interconnects the superimposed layers of the rolled or folded laminate to slow down the unwinding or unfolding process. It is not obvious to one of ordinary skill to combine this feature (inclusion of a liquid-soluble adhesive) with a matrix layer in which at least one of the parameters of width and concentration of active and/or auxiliary substance is not constant in relation to the longitudinal direction of the matrix layer, in order to obtain a device having a release profile that is controlled by the geometry of the active substance-containing layer (width), or the non-uniform concentration of active substance, and the rate of the unrolling process.

Response to Arguments (paragraph 6 of the Office Action)

In paragraph 6 of the Office Action, the Examiner asserts "the concentration of the active agent in relation to the structure of the device is not patentable over the art." It appears that this assertion refers to the limitation "wherein at least one of the parameters of width and concentration of active and/or auxiliary substance is not constant in relation to the longitudinal direction" (see claim 1 of the present invention).

As explained above, using a non-uniform distribution of active substance in the devices of the present invention allows the creation of different release profiles. The Examiner has further asserted that Griffin teaches that the concentration can be changed based on the desired release profile. However, this only means that the overall concentration of the medicament concentration may be different in different embodiments of the device. In any case, however, the medicament is distributed uniformly throughout the sheet, as emphasized repeatedly by Griffin. The devices according to Griffin are designed to unfold or unroll immediately after having arrived in the rumen. To ensure rapid unrolling or unfolding, constraining means are used which are quickly removed in the rumen environment (Griffin at p. 8, lines 15-18). If the sheets of the device should be a little sticky (which would impede the unwinding process), water-soluble coats or water-absorbing sheets are included to eliminate any stickiness and to ensure that the sheet fully unfolds when in the rumen (Griffin at p. 8, 1st par.).

Since the device is fully unfolded when in the rumen, the concentration of active agent in relation to the structure of the device is not of critical importance in the devices described by Griffin. However, the devices of the present invention, due to the presence of adhesive, unroll gradually and are partially unrolled when releasing the active substance (specification at p. 6, 2nd par.), the concentration of active agent in relation to the structure, i.e., longitudinal extension, of the devices of the present invention determines the release profile.

Concerning the "controllable release" of claim 1 of the present invention, both Griffin and Biegajski only teach to vary the overall concentration of active substance, or to use materials having different disintegration or dissolution rates. With these devices, the active substance is released at a more or less constant rate until the layer is fully disintegrated or devoid of active

substance. However, these related art devices are not suitable for releasing active substances with more complex release profile such as described in the present specification (see Fig. 2a/b, Fig. 2c/e; and the description at p. 12, 1st par. of the specification). None of the cited references teaches or suggests how an active substance-containing layer could be "manipulated" to release active agents in any desired controlled release fashion. In particular, these references could not suggest manipulating the active substance-containing layer such that at least one of the parameters of width and concentration of active and/or auxiliary substance is not constant in relation to the longitudinal extension of the layer. Regarding the limiting feature "width ... not constant", it appears that the Examiner has not provided any sound arguments why such modification would have been obvious, and it should be emphasized none of the references suggests an active substance layer having a non-constant width.

As a result, one or ordinary skill in the art would not be motivated by Griffin and Biegajski to produce independent claim 1 of the present invention. A *prima facie* case of obviousness has not been made. Claims depending upon claim 1 are patentable for at least the above reasons.

This rejection is overcome and withdrawal thereof is respectfully requested.

Information Disclosure Statement

The Examiner is thanked for considering the Information Disclosure Statement filed May 22, 2002 and for making the initialed PTO-1449 form of record in the application in the Office Action mailed December 16, 2004.

Foreign Priority

The Examiner has acknowledged foreign priority.

The Drawings

The Examiner is respectfully requested to indicate whether the drawing figures are acceptable in the next official action.

Conclusion

The Examiner's rejection has been overcome, obviated or rendered moot. It is believed that a full and complete response has been made to the Office Action. No issues remain. The Examiner is accordingly respectfully requested to allow the application.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Robert E. Goozner, Ph.D. (Reg. No. 42,593) at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

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RE6

Respectfully submitted,

By _____

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